

Skin Notation (SK) Profile

Propargyl alcohol

[CAS No. 107-19-7]

DRAFT

Department of Health and Human Services
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

This information is distributed solely for the purpose of pre dissemination peer review under applicable information quality guidelines. It has not been formally disseminated by the National Institute for Occupational Safety and Health. It does not represent and should not be construed to represent any agency determination or policy.

Disclaimer

Mention of any company or product does not constitute endorsement by the National Institute for Occupational Safety and Health (NIOSH). In addition, citations to Web sites external to NIOSH do not constitute NIOSH endorsement of the sponsoring organizations or their programs or products. Furthermore, NIOSH is not responsible for the content of these Web sites.

Ordering Information

To receive this document or information about other occupational safety and health topics, contact NIOSH:

Telephone: 1-800-CDC-INFO (1-800-232-4636)

TTY: 1-888-232-6348

E-mail: cdcinfo@cdc.gov

Or visit the NIOSH Web site: www.cdc.gov/niosh

For a monthly update on news at NIOSH, subscribe to *NIOSH eNews* by visiting www.cdc.gov/niosh/eNews.

DHHS (NIOSH) Publication No. XXX

Foreword

As the largest organ of the body, the skin performs multiple critical functions, such as serving as the primary barrier to the external environment. For this reason, the skin is often exposed to potentially hazardous agents, including chemicals, which may contribute to the onset of a spectrum of adverse health effects ranging from localized damage (e.g., irritant contact dermatitis and corrosion) to induction of immune-mediated responses (e.g., allergic contact dermatitis and pulmonary responses), or systemic toxicity (e.g., neurotoxicity and hepatotoxicity). Understanding the hazards related to skin contact with chemicals is a critical component of modern occupational safety and health programs.

In 2009, the National Institute for Occupational Safety and Health (NIOSH) published *Current Intelligence Bulletin (CIB) 61 – A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009-147]. This document provides the scientific rationale and framework for the assignment of multiple hazard-specific skin notations (SK) that clearly distinguish between the systemic effects, direct (localized) effects, and immune-mediated responses caused by skin contact with chemicals. The key step within assignment of the hazard-specific SK is the determination of the hazard potential of the substance, or its potential for causing adverse health effects as a result of skin exposure. This determination entails a health hazard identification process that involves use of the following:

- Scientific data on the physicochemical properties of a chemical
- Data on human exposures and health effects
- Empirical data from in vivo and in vitro laboratory testing
- Computational techniques, including predictive algorithms and mathematical models that describe a selected process (e.g., skin permeation) by means of analytical or numerical methods.

This *Skin Notation Profile* provides the SK assignments and supportive data for propargyl alcohol. In particular, this document evaluates and summarizes the literature describing the hazard potential of the substance and its assessment according to the scientific rationale and framework outlined in CIB 61. In meeting this objective, this *Skin Notation Profile* intends to inform the audience—mostly occupational health practitioners, researchers, policy- and decision-makers, employers, and workers in potentially hazardous workplaces—so that improved risk-management practices may be developed to better protect workers from the risks of skin contact with the chemicals of interest.

John Howard, M.D.
Director
National Institute for Occupational Safety and Health
Centers for Disease Control and Prevention

Contents

FOREWORD	3
ABBREVIATIONS	5
GLOSSARY	7
ACKNOWLEDGMENTS	8
1.0 INTRODUCTION	10
1.1 GENERAL SUBSTANCE INFORMATION:	10
1.2 PURPOSE	10
1.3 OVERVIEW OF SK ASSIGNMENT	10
2.0 SYSTEMIC TOXICITY FROM SKIN EXPOSURE (SK: SYS)	11
3.0 DIRECT EFFECTS ON SKIN (SK: DIR)	12
4.0 IMMUNE-MEDIATED RESPONSES (SK: SEN)	13
5.0 SUMMARY	13
REFERENCES	15
APPENDIX: CALCULATION OF THE SI RATIO FOR PROPARGYL ALCOHOL	17
OVERVIEW	17
CALCULATION	19
APPENDIX REFERENCES	20

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
CIB	Current Intelligence Bulletin
cm ²	square centimeter(s)
cm/hour	centimeter(s) per hour
DEREK	Deductive Estimation of Risk from Existing Knowledge
DIR	skin notation indicating the potential for direct effects to the skin following contact with a chemical
EC	European Commission
GHS	Globally Harmonized System for Labelling and Classification of Chemicals
GPMT	guinea pig maximization test
IARC	International Agency for Research on Cancer
(IRR)	subnotation of SK: DIR indicating the potential for a chemical to be a skin irritant following exposure to the skin
<i>kaq</i>	coefficient in the watery epidermal layer
<i>k_p</i>	skin permeation coefficient
<i>k_{pol}</i>	coefficient in the protein fraction of the stratum corneum
<i>k_{psc}</i>	permeation coefficient in the lipid fraction of the stratum corneum
LD ₅₀	dose resulting in 50% mortality in the exposed population
LD _{Lo}	dermal lethal dose
LLNA	local lymph node assay
LOAEL	lowest-observed-adverse-effect level
log <i>K_{OW}</i>	base-10 logarithm of a substance's octanol–water partition
<i>M</i>	molarity
m ³	cubic meter(s)
mg	milligram(s)
mg/kg	milligram(s) per kilogram body weight
mg/m ³	milligram(s) per cubic meter
mL	milliliter(s)
MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration
REL	recommended exposure limit
RF	retention factor
SEN	skin notation indicating the potential for immune-mediated reactions following exposure of the skin
SI ratio	ratio of skin dose to inhalation dose
SK	skin notation
<i>S_w</i>	solubility

SYS	skin notation indicating the potential for systemic toxicity following exposure of the skin
USEPA	United States Environmental Protection Agency
μL	microliter(s)

DRAFT

Glossary

Absorption—The transport of a chemical from the outer surface of the skin into both the skin and systemic circulation (including penetration, permeation, and resorption).

Acute exposure—Contact with a chemical that occurs once or for only a short period of time.

Cancer—Any one of a group of diseases that occurs when cells in the body become abnormal and grow or multiply out of control.

Contaminant—A chemical that is (1) unintentionally present within a neat substance or mixture at a concentration less than 1.0% or (2) recognized as a potential carcinogen and present within a neat substance or mixture at a concentration less than 0.1%.

Cutaneous (or percutaneous)—Referring to the skin (or through the skin).

Dermal—Referring to the skin.

Dermal contact—Contact with (touching) the skin.

Direct effects—Localized, non-immune-mediated adverse health effects on the skin, including corrosion, primary irritation, changes in skin pigmentation, and reduction/disruption of the skin barrier integrity, occurring at or near the point of contact with chemicals.

Immune-mediated responses—Responses mediated by the immune system, including allergic responses.

Sensitization—A specific immune-mediated response that develops following exposure to a chemical, which, upon re-exposure, can lead to allergic contact dermatitis (ACD) or other immune-mediated diseases such as asthma, depending on the site and route of re-exposure.

Substance—A chemical.

Systemic effects—Systemic toxicity associated with skin absorption of chemicals after exposure of the skin.

Acknowledgments

This document was developed by the Education and Information Division (Paul Schulte, Ph.D., Director). G. Scott Dotson, Ph.D., was the project officer for this document, assisted in great part by Naomi Hudson, Dr.P.H., Loren Tapp, M.D., and Aaron Sussell, Ph.D. The basis for this document was a report (*Toxicology Excellence for Risk Assessment [TERA]*) contracted by NIOSH and prepared by Bernard Gadagbui, Ph.D., and Andrew Maier, Ph.D.

For their contribution to the technical content and review of this document, special acknowledgment is given to the following NIOSH personnel:

Denver Field Office

Eric Esswein, M.Sc.

Division of Applied Research and Technology

Clayton B'Hymer, Ph.D.

John Snawder, Ph.D.

Mark Toraason, Ph.D.

Division of Respiratory Disease Studies

Gregory A. Day, Ph.D.

Aleksander Stefaniak, Ph.D.

Division of Surveillance, Hazard Evaluations, and Field Studies

Matt Dahm, M.Sc.

Todd Niemeier, M.Sc.

Education and Information Division

Devin Baker, M.Ed.

Charles L. Geraci, Ph.D.

Thomas J. Lentz, Ph.D.

Richard Niemeier, Ph.D.

Sudha Pandalai, M.D., Ph.D.

Health Effects Laboratory Division

Stacey Anderson, Ph.D.

H. Fredrick Frasch, Ph.D.

Vic Johnson, Ph.D.

Michael Luster, Ph.D.

Anna Shvedova, Ph.D.

Paul Siegel, Ph.D.

Berran Yucesoy, Ph.D.

National Personal Protection Technology Laboratory

Heinz Ahlers, M.Sc.

This information is distributed solely for the purpose of pre dissemination peer review under applicable information quality guidelines. It has not been formally disseminated by the National Institute for Occupational Safety and Health. It does not represent and should not be construed to represent any agency determination or policy.

Angie Shepherd

**Office of Surveillance, Epidemiology and Laboratory Services/Epidemiology and Analysis
Program Office**

Barbara Landreth, M.A.

In addition, special appreciation is expressed to the following individuals for serving as independent, external reviewers and providing comments that contributed to the development or improvement of this document:

- G. Frank Gerberick, Ph.D., The Procter and Gamble Company, Cincinnati, Ohio
- Dori Germolec, Ph.D., National Toxicology Program, National Institute for Environmental Health Sciences, Research Triangle, North Carolina
- Ben Hayes, M.D., Ph.D., Division of Dermatology, Vanderbilt School of Medicine, Nashville, Tennessee
- Jennifer Sahmel, M.Sc., CIH, ChemRisk, Boulder, Colorado
- James Taylor, M.D., Industrial Dermatology, The Cleveland Clinic, Cleveland, Ohio

1.0 Introduction

1.1 General Substance Information:

Chemical: Propargyl Alcohol

CAS No: 107-19-7

Molecular weight (MW): 56.1

Molecular formula: C₃H₃OH

Structural formula:



Synonyms: 1-Propyn-3-ol; 2-Propyn-1-ol; 2-Propynyl alcohol

Uses: Propargyl alcohol is used primarily as a corrosion inhibitor, chemical reagent and intermediate [ACGIH 2001].

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with propargyl alcohol and (2) the rationale behind the hazard-specific skin notation (SK) assignment for propargyl alcohol. The SK assignment is based on the scientific rationale and logic outlined in the *Current Intelligence Bulletin (CIB) #61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009]. The summarized information and health hazard assessment are limited to an evaluation of the potential health effects of dermal exposure to propargyl alcohol. A literature search was conducted through September 2012 to identify information on propargyl alcohol, including but not limited to data relating to its toxicokinetics, acute toxicity, repeated-dose systemic toxicity, carcinogenicity, biological system/function-specific effects (including reproductive and developmental effects and immunotoxicity), irritation, and sensitization. Information was considered from studies of humans, animals, or appropriate modeling systems that are relevant to assessing the effects of dermal exposure to propargyl alcohol.

1.3 Overview of SK Assignment

Propargyl alcohol is potentially capable of causing numerous adverse health effects following skin contact. A critical review of available data has resulted in the following SK assignment for propargyl alcohol: **SK: SYS (FATAL)-DIR (IRR)**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for propargyl alcohol.

This information is distributed solely for the purpose of pre dissemination peer review under applicable 10 information quality guidelines. It has not been formally disseminated by the National Institute for Occupational Safety and Health. It does not represent and should not be construed to represent any agency determination or policy.

Table 1. Summary of the SK Assignment for propargyl alcohol

Skin Notation	Critical Effect	Available Data
SK: SYS (FATAL)	Acute toxicity	Limited animal data
SK: DIR (IRR)	Skin irritation	Limited animal data

2.0 Systemic Toxicity from Skin Exposure (SK: SYS)

No toxicokinetic data were identified that evaluated the potential of propargyl alcohol to be absorbed through the skin of humans following dermal exposure. Dix et al. [2001] investigated the disposition of propargyl alcohol in male rats following dermal exposure. The authors applied radiolabeled propargyl alcohol in an ethanol solution at the target dose of ~5 milligrams per kilogram (mg/kg) under non-occlude conditions to the backs of test animals for a 6-hour exposure period. When adjusted for body weight, the applied dose corresponded to applied doses of ~1.25 mg/rat. The reported results indicated that only ~5.2% of the applied dose was absorbed through the skin and that up to 85% of the applied dose may be unavailable for dermal absorption because of the volatile nature of propargyl alcohol. In addition, Dix et al. [2001] indicated that it is unlikely that humans would receive a significant internal dose of propargyl alcohol following dermal exposure unless the skin was in contact with liquid propargyl for a prolonged period. The potential of propargyl alcohol to pose a skin absorption hazard was also evaluated, with use of a predictive algorithm for estimating and evaluating the health hazards of dermal exposure to substances [NIOSH 2009]. The evaluation method compares an estimated dose accumulated in the body from skin absorption and an estimated dose from respiratory absorption associated with a reference occupational exposure limit. On the basis of this algorithm, a ratio of the skin dose to the inhalation dose (SI ratio) of 247 was calculated for propargyl alcohol. An SI ratio of ≥ 0.1 indicates that skin absorption may significantly contribute to the overall body burden of a substance [NIOSH 2009]; therefore, propargyl alcohol is considered to be absorbed through the skin following dermal exposure. Additional information on the SI ratio and the variables used in its calculation are included in the appendix.

No human dermal lethal concentration (LD_{Lo}) estimates were identified. A dermal LD₅₀ value (the dose resulting in 50% mortality in the exposed animals) of 88 mg/kg [Vernot et al 1977] was reported in rabbits. In another study, Dow Chemical Company [1957] reported that dermal application of a 1.58% solution of propargyl alcohol in Dowanol 50B at doses of 15.8 mg/kg or 31.6 mg/kg for 24 hours was lethal to 1 of 2 rabbits exposed, while 8 mg/kg produced no toxicity. Signs of toxicity observed included diarrhea and hyperemia [Dow Chemical Company 1957]. Dix et al. [2001] reported no deaths in rats that received ~1.25 mg of propargyl alcohol in an ethanol solution to their backs for 6-hour exposure periods under non-occluded conditions. Because the reported acute dermal LD₅₀ values for rabbits are lower than the critical dermal LD₅₀ value of 200 mg/kg that identifies chemical substances to be considered fatal when in contact with the skin [NIOSH 2009], propargyl alcohol is considered acutely fatal following dermal exposure.

No epidemiological studies or human case reports or repeat-dose, subchronic or chronic dermal toxicity studies in animals were identified that evaluated the potential of propargyl alcohol to cause systemic toxicity following dermal exposure. No standard toxicity or specialty studies were identified that evaluated biological system/function specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposure to propargyl alcohol. Although data were not identified to determine the potential for propargyl alcohol to be carcinogenic following dermal exposure, other agencies or organizations have evaluated the carcinogenicity potential of the substance via alternative exposure pathways. Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for propargyl alcohol.

Table 2. Summary of the carcinogenic designations* for propargyl alcohol by numerous governmental and nongovernmental organizations

Organization	Carcinogenic designation
NIOSH [2005]	No designation
NTP [2011]	No designation
USEPA [2012]	No designation
GHS [European Parliament 2008]	No designation
IARC [2012]	No designation
EC [2012]**	No designation
ACGIH [2001]	No designation

ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; GHS = Globally Harmonized System for Labeling and Classification of Chemicals; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; USEPA = United States Environmental Protection Agency.

*The listed cancer designations were based on data from nondermal (such as oral or inhalation) exposure rather than dermal exposure.

**Date accessed.

Although the single toxicokinetic data identified for propargyl alcohol in rats suggested that the chemical has limited potential to be absorbed through the skin (i.e., percent absorption is less than 10%), this was a non-occluded test, which would not be predictive of absorption following continuous or repeated skin contact. This consideration is supported by the acute dermal toxicity data identified in rabbits [Vernot et al 1977]*, which indicates that propargyl alcohol is potentially fatal when in contact with the skin. Therefore, on the basis of the data for this assessment, propargyl alcohol is assigned the SK: SYS (FATAL) notation.

3.0 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies for corrosivity or *in vitro* tests for corrosivity of propargyl alcohol using human or animal skin models or *in vitro* tests for skin integrity using cadaver skin were identified. Application of 15.8 mg/kg or 31.6 mg/kg of a 1.58% propargyl alcohol solution

*References in **bold** text indicate studies that serve as the basis of the SK assignments.

in Dowanol 50B for 24 hours was reported to cause moderate edema in dermally-exposed rabbits [Dow Chemical Company 1957]. Rowe and McCollister [1982] reported from unpublished data from the Dow Chemical Company, that when applied to the skin of rabbits, the undiluted material caused some superficial necrosis, a 10% solution caused edema, and a 1% solution did not cause any adverse skin effect. The structure activity relationship model, Deductive Estimation of Risk from Existing Knowledge (*DEREK*), predicted propargyl alcohol to be negative for skin irritation. Insufficient data are available to assess the potential of propargyl alcohol to cause skin corrosion. Review of the limited information that is available clearly demonstrates the ability of propargyl alcohol to cause irritation described as moderate edema in human skin and edema in rabbits [Dow Chemical Company 1957]. Therefore, on the basis of the data for this assessment, propargyl alcohol is assigned the SK: DIR (IRR) notation.

4.0 Immune-mediated Responses (SK: SEN)

No occupational exposure studies or human patch tests or predictive tests in animals (guinea pig maximization tests, Buehler test, murine local lymph node assays, etc.) were identified that evaluated the potential of the propargyl alcohol to cause skin sensitization. *DEREK* predicted propargyl alcohol to be a skin sensitizer. Lack of data precludes evaluation of the skin sensitization potential of propargyl alcohol. Therefore, on the basis of the data for this assessment, propargyl alcohol is not assigned the SK: SEN notation.

5.0 Summary

No human data were identified that characterized the toxicological effects of dermal exposure to propargyl alcohol. A single toxicokinetic study for propargyl alcohol in rats suggested that the chemical has limited potential to be absorbed through the skin (i.e., percent absorption is less than 10%) because of the highly volatility nature of the chemical [Dix et al. 2001]. Supplemental evidence from acute dermal toxicity studies in rabbits demonstrated the ability of the chemical to be absorbed in toxicologically significant quantities [Vernot et al 1977]. The findings of these studies indicate that deaths may occur after acute dermal exposure to low concentrations of the chemical. Limited information identified in animals suggests that propargyl alcohol has the potential to be irritating to the skin [Dow Chemical Company 1957]. Insufficient information was identified to assess the potential of propargyl alcohol to cause skin corrosion or act as a skin sensitizer. Therefore, on the basis of these assessments, propargyl alcohol is assigned a composite skin notation of **SK: SYS (FATAL)-DIR (IRR)**.

Table 3 summarizes the skin hazard designations for propargyl alcohol previously issued by NIOSH and other organizations. The equivalent dermal designations for propargyl alcohol, according to the Global Harmonization System (GHS) of Classification and Labeling of Chemicals, are Acute Toxicity Category 3 (Hazard statement: Toxic in contact with the skin) and Skin Corrosion Category 1B (Hazard statement: Causes severe skin burns and eye damage) [European Parliament 2008].

Table 3. Summary of previous skin hazard designations for propargyl alcohol

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption
OSHA [2012] *	[skin]: Potential for dermal absorption
ACGIH [2001]	[skin]: Based on evidence of skin penetration of propargyl alcohol, with subsequent mortality, in treated rabbits
EC [2012] *	R24: Harmful if in contact with skin R34: Cause burns

ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration.

*Date accessed.

References

Note: Asterisks (*) denote sources cited in text; daggers (†) denote additional resources.

*ACGIH (American Conference of Governmental Industrial Hygienists) [2001]. Propargyl alcohol. In: Documentation of threshold limit values and biological exposure indices 7th ed., Vol. 3. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

*Dix KJ, Coleman DP, et al. [2001]. Disposition of propargyl alcohol in rat and mouse after intravenous, oral, dermal and inhalation exposure. *Xenobiotica* 31: 357-375.

*Dow Chemical Company [1957]. Range finding skin absorption tests on propargyl alcohol. By Olson KJ. Midland, MI: Dow Chemical Company. On file with the U.S. Environmental Protection Agency under TSCA Section 8D. OTS #0510183.

*EC (European Commission) [ND]. Prop-2-yn-1-ol. In: EINICS (European Inventory of Existing Commercial Chemical Substances) [<http://esis.jrc.ec.europa.eu/>]. Accessed: 10-01-12.

*European Parliament, Council of the European Union [2008]. Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labeling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJEU, Off J Eur Union L353:1–1355 [<http://eurex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:EN:PDF>]. Accessed: 10-01-12.

†Faucher JA. [1977]. Sorption of organic compounds by human skin. Union Carbide Corporation, Tarrytown, New York. *Cosmet. Toiletries* 92: 61-62.

*IARC (International Agency for Research on Cancer) [2012]. Agents reviewed by the IARC monographs. In: IARC monographs on the evaluation of carcinogenic risks to humans [<http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php>]. Date accessed: 06-06-13.

*NIOSH [2005]. Propargyl alcohol. In: NIOSH pocket guide to chemical hazards. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2005-149 [<http://www.cdc.gov/niosh/npg/>]. Accessed: 06-06-13.

*NIOSH [2009]. Current intelligence bulletin 61: a strategy for assigning new NIOSH skin notations. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2009-147 [<http://www.cdc.gov/niosh/docs/2009-147/pdfs/2009-147.pdf>]. Accessed: 06-06-13.

This information is distributed solely for the purpose of pre dissemination peer review under applicable 15 information quality guidelines. It has not been formally disseminated by the National Institute for Occupational Safety and Health. It does not represent and should not be construed to represent any agency determination or policy.

*NTP [2011]. Report on Carcinogens. Twelfth Edition; U.S. Department of Health and Human Services, Public Health Service. National Toxicology Program [<http://ntp.niehs.nih.gov/ntp/roc/twelfth/roc12.pdf>]. Accessed 10-23-12.

*OSHA [ND]. Propargyl alcohol. In: Sampling and analytical methods [<http://www.osha.gov/dts/sltc/methods/organic/org097/org097.html>]. Accessed: 10-02-12.

* Rowe V; McCollister S.B. [1982]. Alcohols. In: Clayton GD and Clayton FE editors. Patty's Industrial Hygiene and Toxicology, 3rd Rev. ed., Vol. 2C, Toxicology. New York. John Wiley & Sons; 1982. p. 4671-4673.

*USEPA [2012]. Integrated Risk Information System: propargyl alcohol. In: Integrated Risk Information System [<http://www.epa.gov/ncea/iris/subst/0468.htm>]. Accessed: 10-01-12.

Appendix: Calculation of the SI Ratio for Propargyl Alcohol

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for propargyl alcohol. Although the SI ratio is considered in the determination of a substance's hazard potential following skin contact, it is intended only to serve as supportive data during the assignment of the NIOSH SK. An in-depth discussion on the rationale and calculation of the SI ratio can be found in Appendix B of the *Current Intelligence Bulletin (CIB) #61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009].

Overview

The SI ratio is a predictive algorithm for estimating and evaluating the health hazards of skin exposure to substances. The algorithm is designed to evaluate the potential for a substance to penetrate the skin and induce systemic toxicity [NIOSH 2009]. The goals for incorporating this algorithm into the proposed strategy for assigning SYS notation are as follows:

- (1) Provide an alternative method to evaluate substances for which no clinical reports or animal toxicity studies exist or for which empirical data are insufficient to determine systemic effects.
- (2) Use the algorithm evaluation results to determine whether a substance poses a skin absorption hazard and should be labeled with the SYS notation.

The algorithm evaluation includes three steps:

- (1) determining a skin permeation coefficient (k_p) for the substance of interest,
- (2) estimating substance uptake by the skin and respiratory absorption routes, and
- (3) evaluating whether the substance poses a skin exposure hazard.

The algorithm is flexible in the data requirement and can operate entirely on the basis of the physicochemical properties of a substance and the relevant exposure parameters. Thus, the algorithm is independent of the need for biologic data. Alternatively, it can function with both the physicochemical properties and the experimentally determined permeation coefficient when such data are available and appropriate for use.

The first step in the evaluation is to determine the k_p for the substance to describe the transdermal penetration rate of the substance [NIOSH 2009]. The k_p , which represents the overall diffusion of the substance through the stratum corneum and into the blood capillaries of the dermis, is estimated from the compound's molecular weight (MW) and base-10 logarithm of its octanol–water partition coefficient ($\log K_{ow}$). In this example, k_p is determined for a substance with use of Equation 1. A self-consistent set of units must be used, such as outlined in Table A1. Other model-based estimates of k_p may also be used [NIOSH 2009].

Equation 1: Calculation of Skin Permeation Coefficient (k_p)

$$k_p = \frac{1}{\frac{1}{k_{psc} + k_{pol}} + \frac{1}{k_{aq}}}$$

where k_{psc} is the permeation coefficient in the lipid fraction of the stratum corneum, k_{pol} is the coefficient in the protein fraction of the stratum corneum, and k_{aq} is the coefficient in the watery epidermal layer. These components are individually estimated by

$$\begin{aligned}\log k_{psc} &= -1.326 + 0.6097 \times \log K_{ow} - 0.1786 \times MW^{0.5} \\ k_{pol} &= 0.0001519 \times MW^{-0.5} \\ k_{aq} &= 2.5 \times MW^{-0.5}\end{aligned}$$

The second step is to calculate the biologic mass uptake of the substance from skin absorption (skin dose) and inhalation (inhalation dose) during the same period of exposure. The skin dose is calculated as a mathematical product of the k_p , the water solubility (S_w) of the substance, the exposed skin surface area, and the duration of exposure. Its units are milligrams (mg). Assume that the skin exposure continues for 8 hours to unprotected skin on the palms of both hands (a surface area of 360 square centimeters [cm^2]).

Equation 2: Determination of Skin Dose

$$\begin{aligned}\text{Skin dose} &= k_p \times S_w \times \text{Exposed skin surface area} \times \text{Exposure time} \\ &= k_p(\text{cm/hour}) \times S_w(\text{mg/cm}^3) \times 360 \text{ cm}^2 \times 8 \text{ hours}\end{aligned}$$

The inhalation dose (in mg) is derived on the basis of the occupational exposure limit (OEL) of the substance—if the OEL is developed to prevent the occurrence of systemic effects rather than sensory/irritant effects or direct effects on the respiratory tract. Assume a continuous exposure of 8 hours, an inhalation volume of 10 cubic meters (m^3) inhaled air in 8 hours, and a factor of 75% for retention of the airborne substance in the lungs during respiration (retention factor, or RF).

Equation 3: Determination of Inhalation Dose

$$\begin{aligned}\text{Inhalation dose} &= \text{OEL} \times \text{Inhalation volume} \times \text{RF} \\ &= \text{OEL}(\text{mg/m}^3) \times 10 \text{ m}^3 \times 0.75\end{aligned}$$

The final step is to compare the calculated skin and inhalation doses and to present the result as a ratio of skin dose to inhalation dose (the SI ratio). This ratio quantitatively indicates (1) the significance of dermal absorption as a route of occupational exposure to the substance and (2) the contribution of dermal uptake to systemic toxicity. If a substance has an SI ratio greater than or equal to 0.1, it is considered a skin absorption hazard.

This information is distributed solely for the purpose of pre dissemination peer review under applicable 18 information quality guidelines. It has not been formally disseminated by the National Institute for Occupational Safety and Health. It does not represent and should not be construed to represent any agency determination or policy.

Calculation

Table A1 summarizes the data applied in the previously described equations to determine the SI ratio for propargyl alcohol. The calculated SI ratio was 247 is greater than the cutoff point of 0.1. On the basis of these results, propargyl alcohol is predicted to represent a skin absorption hazard.

Table A1. Summary of Data used to Calculate the SI Ratio for propargyl alcohol

Variables Used in Calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(k_{psc})	cm/hour	1.2734×10^{-3}
Permeation coefficient of the protein fraction of the stratum corneum (k_{pol})	cm/hour	2.0286×10^{-5}
Permeation coefficient of the watery epidermal layer (k_{aq})	cm/hour	0.3337
Molecular weight (MW) ^a	amu	56.07
Base-10 logarithm of its octanol–water partition coefficient ($\text{Log } K_{ow}$) ^a	None	-0.38
Calculated skin permeation coefficient (k_p)	cm/hour	1.2887×10^{-3}
Skin dose		
Water solubility (S_w) ^a	mg/cm ³	1000
Calculated skin permeation coefficient (k_p)	cm/hour	1.2887×10^{-3}
Estimated skin surface area (palms of hand)	cm ²	360
Exposure time	hour	8
Calculated skin dose	mg	3711.38
Inhalation Dose		
Occupational exposure limit (OEL) ^b	mg/m ³	2
Inhalation volume	m ³	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	15
Skin dose–to–inhalation dose (SI) ratio	None	247.43

^aVariables identified from SRC [2009].

^bThe OEL used in calculation of the SI ratio for propargyl alcohol was the NIOSH recommended exposure limit (REL) [NIOSH 2005].

Appendix References

NIOSH [2005]. NIOSH pocket guide to chemical hazards. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2005-149 [http://www.cdc.gov/niosh/npg/]. Accessed: 03-08-11.

NIOSH [2009]. Current intelligence bulletin 61: a strategy for assigning new NIOSH skin notations. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2009-147 [http://www.cdc.gov/niosh/docs/2009-147/pdfs/2009-147.pdf]. Accessed: 03-08-11.

SRC [2009]. Interactive PhysProp database demo [<http://www.srcinc.com/what-we-do/databaseforms.aspx?id=386>]. Accessed: 03-08-11.